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Invited Editorial: Mapping Dysmorphic Syndromes with the Aid of the Human/Mouse Homology Map

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In this issue of the *Journal* the paper by Foy et al., which maps Waardenburg syndrome type 1 to 2q37, is an excellent example of the potential usefulness of the human/mouse homology map. It would be an even better example if the authors had chosen to search this chromosomal region solely on the basis that the *splotch* mutation of mice provides a disease homologue for Waardenburg syndrome. While the results argue strongly that *splotch* does provide such an homology, Foy et al. also searched this area because of the recent report by Ishikiriyama et al. (1989) that an inversion of 2q35 to 2q37 was associated with a new mutation to Waardenburg syndrome type 1. Nonetheless, rapid advances in gene mapping in both species are steadily increasing the usefulness of this approach for mapping dysmorphic syndromes. Over 300 loci have now been assigned to chromosomes in both man and mouse. These assignments are available in several different formats. Article-length updates of the comparative maps have been presented in journals at intervals. The most recent is that by Searle et al. (1989). Staff members at the Jackson Laboratory continually update the "locus map of mouse with comparative map points of human on mouse." The most recent version of this is available from A. L. Hillyard, D. P. Dolittle, M. T. Davisson, and T. H. Roderick (Jackson Laboratory, Bar Harbor, ME 04609). This is also published at frequent intervals in *Mouse Genome* (a continuation of *Mouse News Letter*), which is currently printed by Oxford University Press.

Most of the homologous loci mapped are for enzymes or DNA sequences. Many genes involved in morphogenesis, and for which mutations may result in dysmorphic diseases, are highly conserved in mammals. A good example is the extraordinary similarity in phenotypes for genes involved in pigmentation (Searle 1968). However, the differences in amount of body hair, basal pigmented state, and overall form of limbs and facial structures, for instance, between mouse and man prevent ready assignment of homologous morphogenic loci. Inasmuch as the X chromosome shows the greatest evolutionary conservation and sex linkage is easily detected, X chromosomal maps are accordingly more developed. Thus, it is on the X chromosome that homology of position has allowed greater certainty as to homology of dysmorphic disease states. For instance, *Tabby* (*Ta*) seems clearly homologous to hypohidrotic ectodermal dysplasia. *Ta* hemizygotes have marked abnormalities of their hair (Kindred 1967), a marked reduction in the size of the teeth (Grünberg 1966), and absence or reduction in size of some exocrine glands, including the epidermal growth factor (EGF)–secreting submandibular gland (Blecher et al. 1983). It is important to note that anhidrosis and absence of sweat glands have been demonstrated in mice hemizygous for *Ta* (Blecher 1986). The case of homology is supported by conservation of the flanking loci for testicular feminization and *Pgk*-1. Recently, evidence has been presented that exogenous EGF can promote development of functional sweat glands in *Ta* homizygotes (Blecher et al., in press) a finding which could have relevance for human hypohidrotic ectodermal dysplasia if true homology were to be established. On the other hand, although Happle et al. (1983) have argued that *Bare-patches* (*Bpa*) is homologous to X-linked chondrodysplasia punctata, the comparative mapping does not confirm the homology. Happle et al. (1983) found microscopic evidence for premature foci of calcification in the heterozygous *Bpa*/+ mice *in utero*, cataracts, a hyperkeratotic eruption in pups turning to bare patches arranged in a linear and blotchy pattern in older mice, and occasional linear pigmentary disturbances. However, X-linked

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chondrodysplasia punctata has been mapped to Xp (Curry et al. 1984), while *Bpa* maps near G6PD, i.e., a region homologous to Xqter. The timing and appearance of skin abnormalities, as well as the presence of eye abnormalities, allows one to consider Bare-patches as a homologue of incontinentia pigmenti (IP). *Striated* (Phillips 1963), which maps near to Bpa, shows stripes of depigmentation, and it might also be considered a candidate for IP, but the location of IP at Xp11 in man, as revealed by X-autosomal translocations (Hodgson et al. 1985; Cannizaro and Hecht 1987), better fits the location of *Tattered* (Davisson 1987). The mapping of familial cases of IP to Xq (Sefiani et al. 1988) is homologous to the location of *Bpa* and *striated*. Thus, *striated* or *Bpa* may be homologous to one form of IP. In contrast to the problem in choosing the correct disease homologue for *Bpa*, the X-linked morphological mutations with known biochemical defects have led to clear-cut homologous assignments: *sparse fur* is a mutation at the ornithine transcarbamylase locus (deMars et al. 1976), while *Mottled-brindled* shows abnormalities of copper metabolism similar to those found in Menkes syndrome (Camakakis et al. 1980).

If it is freuquently difficult to define homologous morphogenic loci on the X chromosome, it is even more difficult to do so for autosomal loci when there are so many more candidate loci for homology. Several good candidates for homologous morphogenic mutants have been found. The dominantly inherited form of aniridia, which is linked to human 11p (Simeola et al. 1983), seems homologous to the mouse mutation *Small eye* (*Sey*), which maps to mouse chromosome 2 in a region with several other 11p markers. Greigs cephalopolysyndactyly appears to be homologous to *Extra toes*. It is a syndrome with a high cranial vault, prominent forehead, and polysyndactyly and which may map to 7p, since two cases found associated with balanced translocations shared a breakpoint at 7p13 (Winter and Huson 1988). The mouse mutant *Extra toes* has polydactyly and an enlarged interfrontal bone and maps to chromosome 13 adjacent to T-cell receptor gamma, which maps in man to 7p13. However, the homologies of mapping position are essential for both of these assignments. For instance, polydactyly also occurs in a number of other mouse mutations (*Ed, hop*^{hpy}, *Hx, pcp, Pdn, Po, Ps, Pst, py, ty, Xp1,* and *Xs*—which include mutants mapping to a variety of chromosomes). This difficulty in choosing the correct homologous mouse mutation is also exemplified by Waardenburg syndrome, for which candidate loci other than *splotch* exist. *White* (*Mi*^{wh}) shows, in heterozygous condition, a slight reduction in iris and choroid pigment, variable white spotting, and inner ear abnormalities with a reduction in hair cells (Deol 1967). *Piebald* (*S*) has white spotting and megacolon (which occurs in Waardenburg syndrome type I). The homozygote for a lethal allele (S^1) has inner ear abnormalities similar to those seen in *Mi*^{wh}/+ (Deol 1967). Useful tools to aid in searching for homologous dysmorphic disease loci are Kalter's compendium of genetic congenital malformations in mice (Kalter 1980) and a mouse malformation data base (Winter 1988).

Another useful aspect of the mouse/human homology map is the more advanced analysis of germ-line imprinted regions available for the mouse map. Germline (or chromosomal) imprinting is a classic concept in genetics, one derived from studies of chromosomal elimination in *Sciara*—the set of chromosomes eliminated was always the paternal one, and therefore it was believed that passage through the paternal germ line provided information to—i.e., imprinted—the chromosomes (Crouse 1960). The first example studied in mammals concerns the X chromosome. It was found some time ago that in marsupials the paternal X is preferentially inactivated (Cooper 1971), certainly in readily accessible tissues such as blood and perhaps in many other tissues. In eutherians it was found that the paternal X is preferentially inactivated in extraembryonic membranes (Takagi and Sasaki 1975). In fact, such germline imprinting as first found for the X and now well demonstrated for many chromosomal regions in mice explains the failure of parthenogenesis in mammals. The mouse imprinting map is updated in *Mouse News Letter* by Beechey et al. (1989). This map can be used to see whether the homologous mutants for human disorders lie in regions subject to genomic imprinting. It has recently become clear that Angelman and Prader-Willi syndromes share similar deletions but with different parental origins (Knoll et al. 1989) and that nondeletion Prader-Willi syndrome patients frequently show maternal isodisomy for 15q12 (Nicholls et al. 1989). Prader-Willi syndrome may be the result of the lack of a paternal imprinted copy of 15q12, while Angelman syndrome may be due to the absence of the maternal imprinted copy. Several proximal 15q loci have homologous loci near the center of mouse chromosome 2, a region which has not been shown to be imprinted, but the homology map is not very complete in the region 15q12. On the other hand, the distal 4p locus, D4S10, maps to mouse chromosome 11 (Searle et al. 1989) in a region showing genomic imprinting. This may be relevant to the appearance of childhood-onset

Huntington disease when the father transmits the gene but not when it has a maternal origin (Erickson 1985).

I have chosen to use examples of dysmorphic disease for this editorial on the usefulness of the human/mouse homology map because of its relevance to the report by Foy et al. (1990) in this issue of the *Journal*. However, examples could have been used for neurological, hematological, cardiac, or gastrointestinal mutants. Many of the hematological mutants have precise homologies recognized because of shared mutant proteins, e.g., hemoglobin, spectrin, etc. It has been harder to recognize homologous neurological mutations, perhaps because of the difference in complexity of the two central nervous systems and because mouse geneticists have studied behavioral variations less than have human geneticists. For instance, all mice of the C3H strain are blind after 6 wk of age because the *retinal degeneration* mutation has been fixed in this inbred line. However, it took mouse geneticists 20 years to recognize the blindness.

In conclusion, it can be predicted that, as molecular techniques become more widely applied in human genetic studies, murine homologies of human disorders, such as that reported by Foy et al. in this issue of the *Journal*, will play an increasingly important role in enhancing our understanding of the human genome.

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